COURAGE Chronicle

April 2000

COURAGE SERIOUS ADVERSE EVENT (SAE) REPORTING

Since no SAE's have been reported to date, there is a concern that confusion exists as to when to complete a COURAGE SAE Report. In this study, an event is "serious" when the patient outcome is or involves:

- Death
- Disability (persistent or substantial disability)
- Admission to an inpatient hospital
- Prolongation of an existing inpatient hospitalization
- Congenital anomaly in the offspring of the study pt.
- Development of cancer (Req'd by Merck)
- Overdose - intentional or accidental (Req'd by Merck)
- A life threatening event (i.e., in the view of the reporter, the patient was at a real immediate risk of death as the event occurred, i.e., severe bradycardia)

The COURAGE Serious Adverse Event Report (Form 18) must be completed for any serious adverse event (SAE) judged by the investigator to be **reasonably attributable** to one of the donated study drugs. Thus, a Form 18 will not be required for ALL SAEs, only those felt to be reasonably attributable to one or more of our study drugs.

An example of an SAE that must be reported on Form 18 is a patient hospitalized for severe bradycardia. This SAE could be associated with Toprol XL® - an SAE report must be completed. When a patient is hospitalized for a right BKA (below the knee amputation), a COURAGE SAE report is not required, since this event is not felt to be reasonably attributable to any of the study drugs.

If you have a question about whether to complete Form 18 for an SAE, please contact Carol Fye, Study Pharmacist, or one of the Study Co-Chairmen.

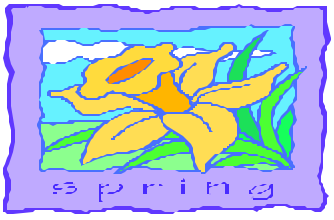
Left Ventricular Ejection Fraction ...

Significant problems are apparent concerning incomplete, missing or technically unsatisfactory left ventricular (LV) ejection fraction (EF) measurements on certain patients randomized to the COURAGE Trial.

In particular, we continue to receive information from Dr. Mancini's Coronary Angiography Core Lab that certain cineangiographic measurement of EF, submitted on Form 02 by the COURAGE site investigators, are technically unsatisfactory from the Core Lab perspective (generally because of PVCs).

Since LVEF is widely known to be an important, independent determinant of prognosis in patients with symptomatic CHD, it is essential that we have as complete data as possible on EF measurements. If you receive notice form the Coronary Angiography Core Lab that a cineangiographically-derived LVEF measure is technically unsatisfactory, **you must obtain** a non-invasive assessment of LVEF (preferably with radionuclide ventriculography or with quantitative 2DE) as a surrogate measure within 30 days of notification, in the absence of an intercurrent clinical event. If, for clinical reasons, a cineangiographic LVEF measurement is not obtained, or there are PVCs present, you should perform a non-invasive LVEF as soon as possible in order to minimize any delays in obtaining needed LV function assessments.

When a surrogate, non-invasive measure of LVEF is obtained, please resend these results to the West Haven Coordinating Center, not to Dr. Mancini's Coronary Angiography Core Lab.



PATIENT RANDOMIZATION UPDATE

Audie Murphy VAMC – San Antonio	44
London Health Science Centre	30
Ann Arbor VAMC	27
Montreal Heart Institute	26
Houston VAMC	23
Durham VAMC	21
Queen Elizabeth II HSC	16
Mid America Heart Institute	15
Mayo Clinic	14
Sunnybrook & Women's College HSC	13
Little Rock VAMC	13
Seattle VAMC	13
Foothills Hospital	13
Lexington VAMC	12
New York VAMC	12
Iowa City VAMC	11
Emory University Hospital	10
Albuquerque VAMC	10
Toronto Hospital	9
Univ. of Michigan Medical Center	9
University of Oklahoma HSC	8
Atlanta VAMC	7
Nashville VAMC	7
Univ. of Alberta Hospital	7
St. Paul's Hospital	6
Boston Medical Center	6
SUNY HSC	5
Hamilton General Hosp./McMaster Univ	4
Cleveland Clinic Foundation	4
Sudbury Memorial Hospital	3
Barnes-Jewish Hospital	3
Vanderbilt University	2
Vancouver Hospital and HSC	2
St. Michael's Hospital	1
Christiana Care Health Systems	1
MIMA Century Research Associates	1
Total Patients as of 4/7/00	**408**

NUCLEAR SUBSTUDY

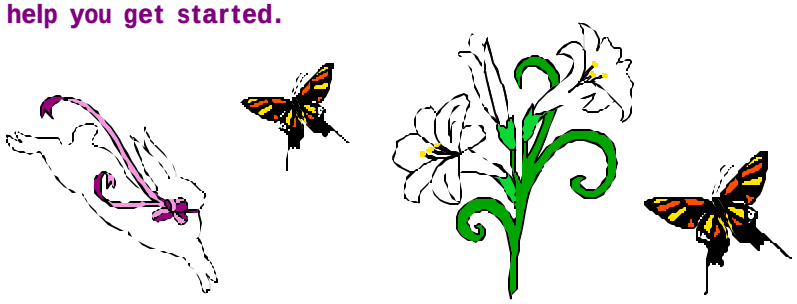
COURAGE Substudy: Nuclear substudy II: Short-term Effects of Medical and Interventional Therapy on Ischemic Burden as Determined by Perfusion SPECT Imaging in Patients Enrolled in the COURAGE Trial is currently in the start-up phase.

Thanks to DuPont for sponsoring the kick-off meeting on March 13th during the ACC meeting to discuss the final details and to the investigators and the study coordinators for their attendance and input. Sites interested in the substudy will receive a summary of the issues discussed.

Also of note…

- IRB/REB approval, independent of the approval for the main trial, is required for you to conduct this substudy. Please keep us updated on your progress.
- We are happy to announce that there is funding for the study:
  - $300 for the baseline SPECT
  - $300 for the follow-up SPECT
  - Free sestamibi and free adenosine for both studies

We are still recruiting sites to participate in this important substudy. For more information, please call Kate Hanson (ph: 404-727-9235) at Emory or Tara Gurtler or Lisa Miranda (ph: 310/423-4387) at Cedars-Sinai. We can provide you with a protocol, a template informed consent, and other information to help you get started.



REMINDER: USE COURAGE STUDY DRUGS & FAX DRUG INVENTORY REPORTS TO PCC EVERY 2 WEEKS

Toprol XLÒ Usage: Answers to some questions received by COURAGE PCC concerning Toprol XL®:
When switching a patient from the immediate release metoprolol tablets to the extended release formulation (Toprol XL®), AstraZeneca recommends that the same daily dose of Toprol XL® be prescribed; i.e., if a patient was taking 75 mg BID (150mg/day) of the immediate release formulation, then 150mg / day of Toprol XL® should be prescribed.

Canadian sites: ImdurÒ - Imdur® 30mg tablets are not marketed in Canada; therefore, only the 60mg tablets have been provided by AstraZeneca Canada for the Canadian sites.